Ketone Metabolism

Keto Acids

Adipose, muscle, and liver can use fatty acids, oxidize them in their mitochondria, and generate energy. Red blood cells have no mitochondria and can't use keto acids. Brain cells are too busy, so they also can't oxidize fatty acids themselves. But the acetyl-CoA of fatty acids can still provide energy in another form. "Fat energy" comes from oxidation (in the liver) and from ketone bodies (from the liver). **Only liver cells can make keto acids**. Any cell **with a mitochondrion can use keto acids**. Those with the most metabolic demands (skeletal muscle, brain, and renal cortex—cells of the tubules) are the most likely to benefit from ketones.

Ketogenesis occurs in hepatocytes during the **glucagon-dominant** state, when the **liver is flush with energy**. It requires excess **acetyl-CoA** in the mitochondria. It coincidentally occurs in the hormone state and organelle where **fatty acid catabolism** has just occurred. As we learned, fatty acid catabolism produces a tremendous amount of **energy** (NADH, $FADH_2$) and **acetyl-CoA**—so much that any acetyl-CoA would have already gone down the TCA-ETC and generated more energy. In the mitochondrion, there's a branch-point for acetyl-CoA. Acetyl-CoA goes through TCA-ETC if the hepatocyte's own energy is spent, so that it can perform gluconeogenesis; OR acetyl-CoA goes to making ketone bodies in a hepatocyte with excess energy.

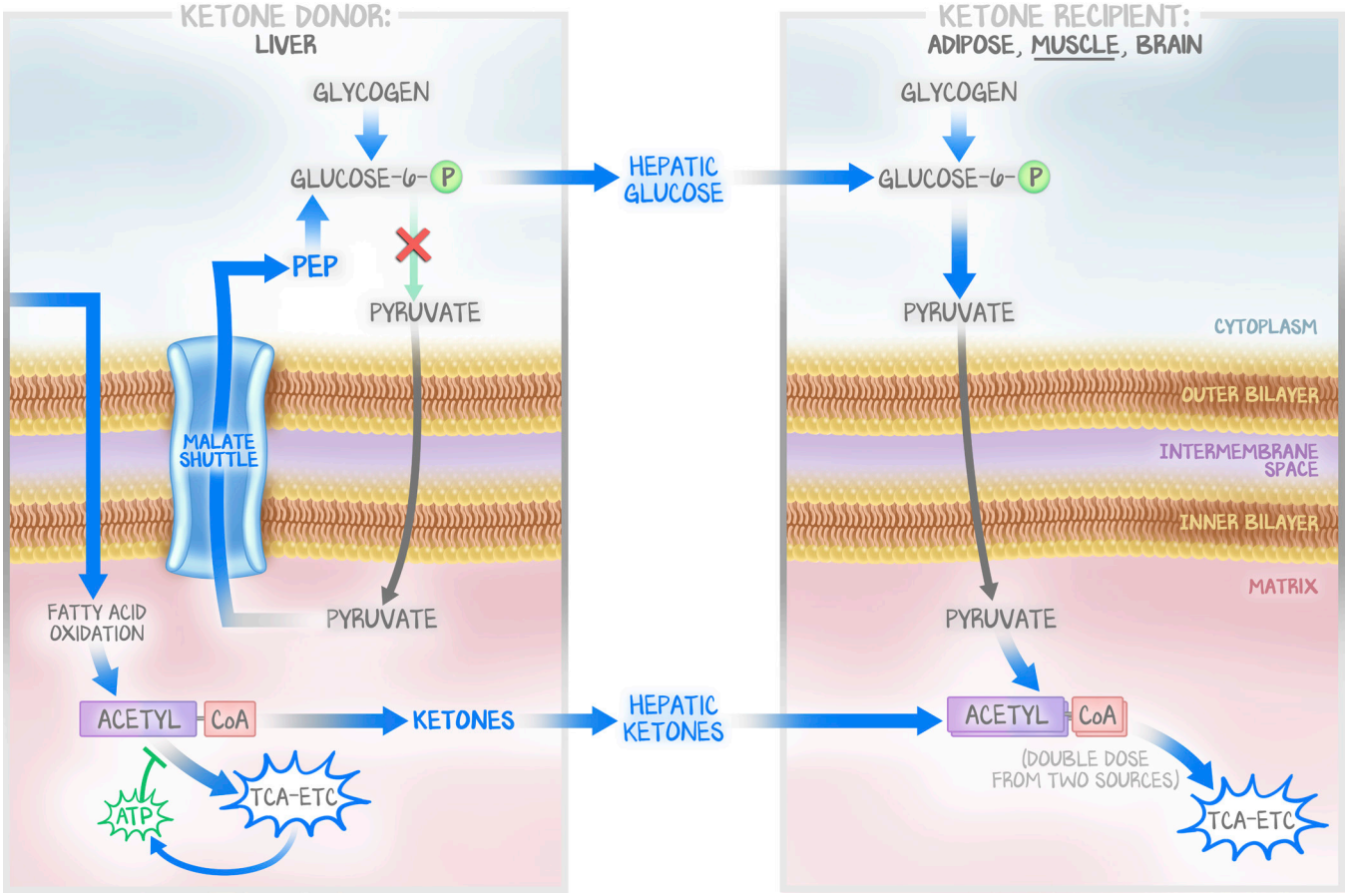

Figure 16.1: The Liver Supplies Energy
Excess energy (acetyl-CoA) in the liver generated from fatty acid oxidation can be transported to extrahepatic tissues in the form of ketones. The liver supplies glucose through gluconeogenesis and acetyl-CoA as ketones.

The idea here is that **excess acetyl-CoA** is packaged and distributed to the body where they are taken up by cells to be turned back into acetyl-CoA—substrate for TCA-ETC even in the absence of glucose to burn through glycolysis.

Acetyl-CoA comes from β oxidation of fatty acids in the mitochondria. Acetyl-CoA can also come from ketones in the mitochondria. All cells can use glucose. All cells with a mitochondrion can use ketone bodies. Only the liver (and to a limited extent, skeletal muscle) can oxidize fatty acids. Ketones are how all tissues (except RBCs) can "use fat."

Ketogenolysis occurs in **extrahepatic tissues**. Circulating ketones are picked up by tissues as ketone bodies, which are then **activated in their mitochondria**, and reform the original acetyl-CoA. These acetyl-CoA are then placed in the TCA-ETC to generate ATP.

Enzymes of Ketogenesis

Acetyl-CoA is turned into **HMG-CoA** by **HMG-CoA synthase**. This is the same step in cholesterol metabolism, only cholesterol metabolism is **in the cytoplasm**. Keeping the two pathways regionally distinct is important. Cholesterol synthesis is for when there is an abundance of carbon and energy, when insulin is dominant. Ketogenesis occurs when glucagon is dominant—the exact wrong time for cholesterol metabolism. While they do share this step, the two pathways never encounter each other, nor do they compete with or regulate each other.

This is also why we discuss cholesterol synthesis in cardiology—separately, so they're not learned together.

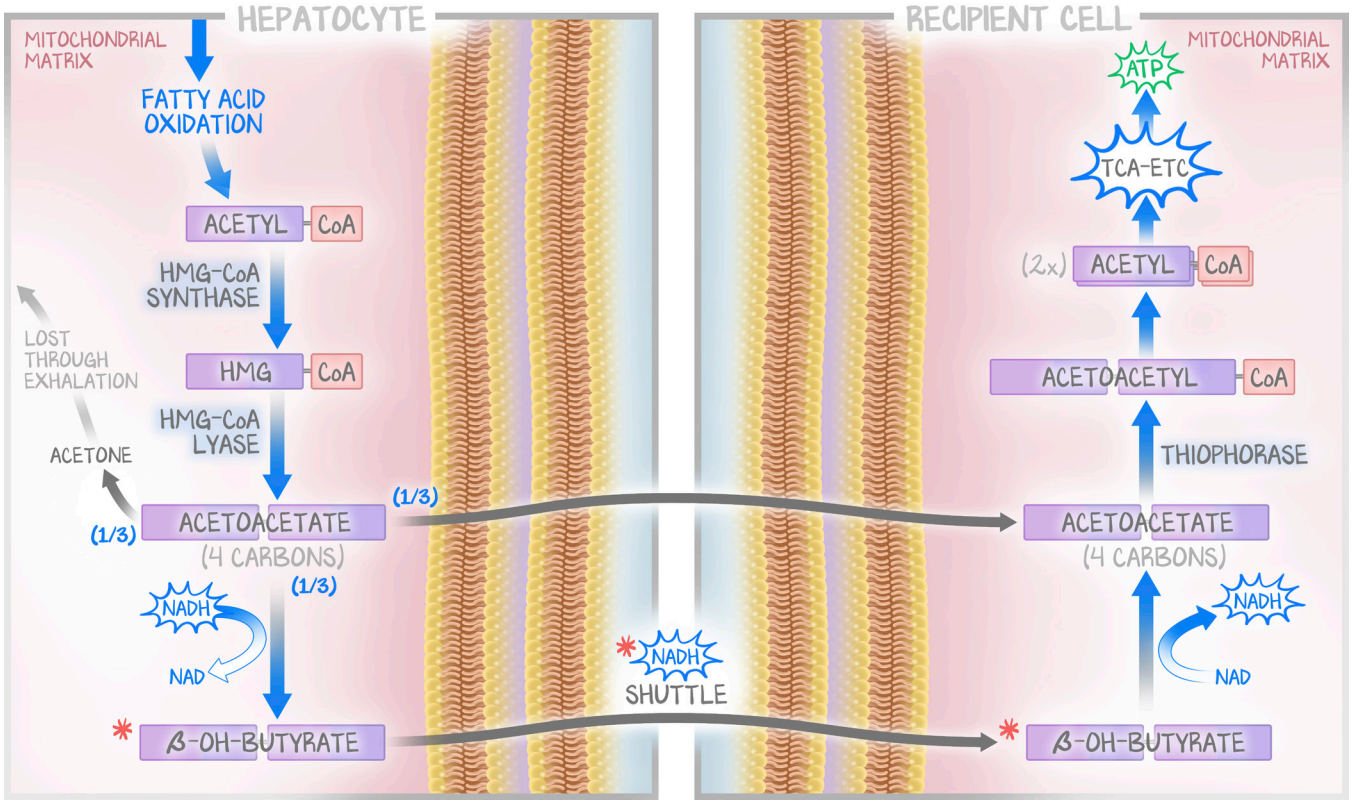

Figure 16.2: Ketone Pathways
The liver takes acetyl-CoA and turns it into ketones. Either as acetoacetate or the extra-energy-containing β-hydroxybutyrate, these ketones circulate to extrahepatic tissues where they are turned back into acetyl-CoA.

HMG-CoA is then turned into **acetoacetate**. This step is NOT seen in cholesterol metabolism and is unique to the mitochondria and formation of ketones. **Acetoacetate** itself can **transfer throughout the body**, where it's activated in the mitochondria of the receiving cell, turned into **acetoacetyl-CoA** (a four-carbon sugar), and then broken into two acetyl-CoA. One-third of acetoacetate circulates as acetoacetate. One-third of acetoacetate is turned into acetone. **Acetone** is unstable and **lost through exhalation**. It has no metabolic consequence—it provides no energy and is simply lost. However, in the state of ketoacidosis (below) where excess ketones are being made, acetone is responsible for the **sweet fruity odor** of an affected person's breath. Clinically relevant in practice, it isn't part of our discussion in biochemistry. The final third of acetoacetate is circulated as **β-hydroxybutyrate**, a **higher-energy** form of acetoacetate.

β-Hydroxybutyrate is made in a hepatocyte that is undergoing β oxidation of fatty acids. There's a lot of NADH and $FADH_2$ being made, meaning the cell is in a high-energy state. Fatty acid oxidation also means a lot of acetyl-CoA. The liver's job is to get energy out to tissues in the periphery, doing that by way of gluconeogenesis and ketone bodies. The most clever thing the liver could do is send energy with compounds that can generate more energy. Acetoacetate is two acetyl-CoA. Those are "compounds that can generate more energy." But there's no extra energy attached to acetoacetate. Since the NADH is so abundant, the liver uses **excess NADH within itself** to make **β-hydroxybutyrate**. Once it gets to the receiving cell, it's turned back into acetoacetate, **releasing the NADH** in the receiving tissue. It's almost as if the β-hydroxybutyrate were a shuttle for the NADH. The receiving cell still gets the two acetyl-CoA from β-hydroxybutyrate, but it also gets an extra NADH along for the ride.

Enzymes and Substrates of Ketogenolysis

Acetoacetate is activated in the mitochondria by **succinyl-CoA acetoacetyl-CoA transferase** (commonly called **thiophorase**). This enzyme **is not in hepatocytes**—otherwise the liver would just use the ketone body it just made. The β-hydroxybutyrate is oxidized first by a dehydrogenase to recover the NADH, before it's acetoacetate.

How the Brain Uses Ketones During Prolonged Starvation

The brain is metabolically active, doesn't oxidize fatty acids, and stores no glycogen. It needs a constant supply of energy either in the form of glucose or ketones.

On the **first day of a fast**, the brain **prefers glucose**. This glucose is created by the **liver** via **glycogenolysis**. The liver shifts from the insulin-dominant to the glucagon-dominant world. The most easily accessible form of energy is glycogen. At the same time, the liver starts oxidizing fatty acids (making ketones) and starts gluconeogenesis.

On the **first week of a fast**, the brain **still prefers glucose**. Since the person is fasting, the glycogen stores deplete fairly rapidly, and the brain is dependent on **gluconeogenesis** for its glucose. We already learned that most fatty acids, all that are even-chained, **can't become glucose**. They can provide the energy such that the liver is capable of making glucose, but fatty acids can't be changed into glucose. With glycogen stores depleted and no nutritional glucose coming into the body, the only source of carbon for gluconeogenesis is **protein catabolism**. We've yet to discuss, but suffice it to say that ongoing protein catabolism might provide the brain with its desired glucose, but will very rapidly rob the organism of the ability to get more glucose.

So **after the first week of a fast**, there's a catabolic switch. The brain prefers glucose, **but switches to a ketone-use state**. Ketones can be made from fats. Fats are able to be sacrificed rather than lose protein. The longer the fast goes on, the less glucose is made from gluconeogenesis because less protein is being catabolized. Instead, fats are depleted.

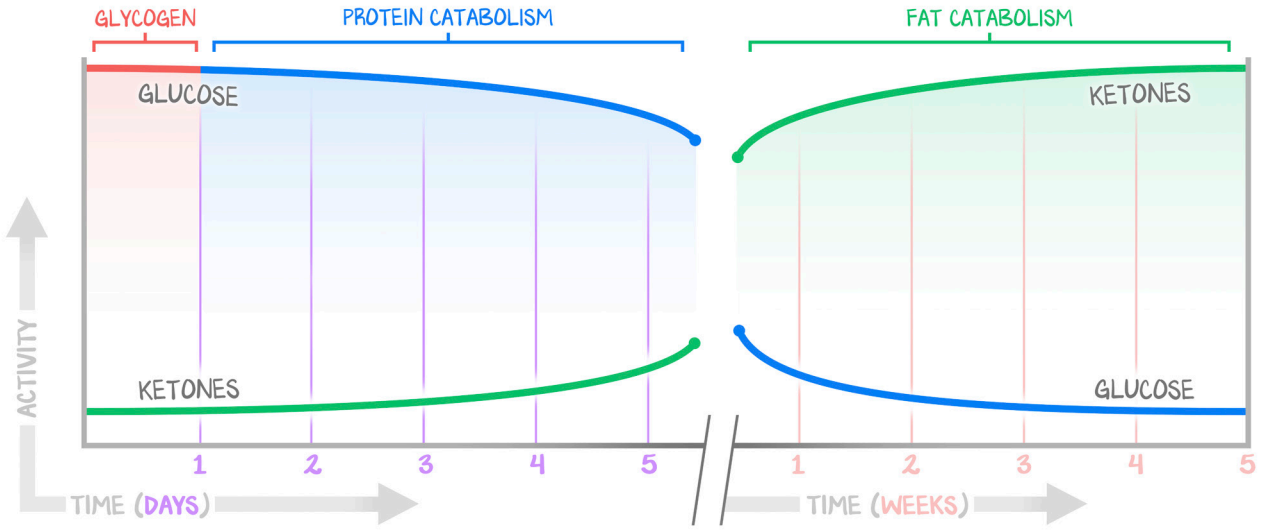

Figure 16.3: Starvation and Energy Sources
Hepatic glycogen supports the use of the brain's glucose for a day, then protein catabolism supports hepatic gluconeogenesis for the brain's glucose for about a week. After that, the body switches to supply the brain with primarily ketones from fat catabolism.

Ketoacidosis

After the first week of a fast, the brain uses ketones. **Ketones** are **acidic**. Too much of them and they will cause an **acidemia**. This can be detected by finding a **decreased serum bicarbonate** and a **pH < 7.4**. Other acids can do this, of course, and ketones are only one such acid. But "fast" is another word for "starve." **Starvation ketosis** occurs when the body **is or feels starved of glucose**.

Actual starvation is more obvious: cachexia, edema, low albumin, and wasting. Some situations may be slightly less obvious. **Chronic alcoholics** who get all their calories from alcohol will not have access to glucose. Those who are **starving** because of lack of access to food (elderly, poor) or those who are lost and cannot find a nutritional source (environmental) will recruit the use of **ketones**. This is what we described in the last section on prolonged starvation.

A body might "feel starved" of glucose if there's a lot of glucose in the blood, but the cells can't see it or access it. This is the case of **patiens with type 1 diabetes** who **don't take their insulin**. Having no endogenous production of insulin, regardless of the glucose levels in their blood, no matter how "off" glucagon is, if there's **no insulin there can be no glucose uptake**. Yes there are basal channels, but that can't meet the metabolic demand of tissue. Yes, skeletal muscle can take up glucose on exercise. But overall, and especially to the brain, **there effectively is no glucose**. So the body switches to ketones. The osmotic load the glucose brings dehydrates the patients (more in Endocrine) and the **ketoacidosis makes them acidotic**. Both are bad. Acidosis causes **encephalopathy** and causes the **sympathetic nervous system to fail**—blood vessels will not constrict during acidemia while they are volume-depleted. **D**iabetic **k**eto**a**cidosis (DKA) is a problem both with volume (give lots of fluids) and nutrition (give insulin to reduce the acidosis). Patients with type 2 diabetes almost never go into DKA—whatever small amount of insulin activity they have is enough to prevent ketoacidosis. They still get sick and dehydrated, though. Hyperglycemic hyperosmolar **nonketotic** coma is life-threatening, but the patient will have **no ketones** and a **normal pH**.

The diagnosis of DKA is often made clinically—type I diabetes, hyperglycemia, juicy sweet breath (the acetone)—but confirmation of DKA can be made by looking for ketones—**β-hydroxybutyrate** in the blood or urine and an arterial blood gas confirming a lowered pH.

For patients with **moderate acidemia** and **ketones**, think either type 1 diabetes (which should be more obvious clinically) or relative starvation ketosis (you can be overweight and ketotic).